Answer 1:

Bibliographic Information

Restoring chemotherapy and hormone therapy sensitivity by parthenolide in a xenograft hormone refractory prostate cancer model. Shanmugam, Rajasubramaniam; Jayaprakasan, Vetrichelvan; Gokmen-Polar, Yesim; Kelich, Stephanie; Miller, Kathy D.; Yip-Schneider, Michele; Cheng, Liang; Bhat-Nakshatri, Poornima; Sledge, George W., Jr.; Nakshatri, Harikrishna; Zheng, Qi-Huang; Miller, Michael A.; DeGrado, Timothy; Hutchins, Gary D.; Sweeney, Christopher J. Department of Medicine, Indiana University, Indianapolis, IN, USA. Prostate (Hoboken, NJ, United States) (2006), 66(14), 1498-1511. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. CAN 147:1016 AN 2006:1117125 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Nuclear Factor kappa B (NFκB) is a eukaryotic transcription factor that is constitutively active in human cancers and can be inhibited by the naturally occurring sesquiterpene lactone, parthenolide (P). The in vitro effects of P were assessed using the androgen independent cell line, CWR22Rv1, and human umbilical endothelial cells (HUVECs). The in vivo activity of P as a single agent and its ability to augment the efficacy of docetaxel and the anti-androgen, bicalutamide, were detd. using the CWR22Rv1 xenograft model. Parthenolide at low micromolar concn. inhibited proliferation of CWR22Rv1 and HUVEC cells, promoted apoptosis and abrogated NFκB-DNA binding. Parthenolide downregulated anti-apoptotic genes under NFκB control, TRAF 1 and 2, and promoted sustained activation of c-jun-NH2 kinase (JNK). Parthenolide also augmented the in vivo efficacy of docetaxel and restored sensitivity to anti-androgen therapy. These studies demonstrate parthenolide's anti-tumor and anti-angiogenic activity, and its potential to augment the efficacy of chemotherapy and hormonal therapy.

Answer 2:

Bibliographic Information

Studies with CWR22 xenografts in nude mice suggest that ZD1839 may have a role in the treatment of both androgen-dependent and androgen-independent human prostate cancer. Sirotnak, Francis M.; She, Yohung; Lee, Fei; Chen, Jing; Scher, Howard I. Program in Molecular Pharmacology and Therapeutics and Genitourinary Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. Clinical Cancer Research (2002), 8(12), 3870-3876. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 139:143462 AN 2002:974069 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

These studies examd. the effect of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor ZD1839 (Iressa) on CWR22 prostate tumors in nude mice. The effect of ZD1839 was also examd. in combination with either bicalutamide (Casodex) or cytotoxic agents against a hormone-dependent or -independent variant of CWR22, resp. The xenografts were grown for 4-7 days, then tumor measurements were made and therapy initiated. ZD1839 and bicalutamide were given p.o. on a once-daily, 5-day schedule for 2 successive weeks. Carboplatin and paclitaxel were given every 3-4 days for a total of four doses. Measurements of tumor vol. were made twice weekly during treatment and for 2 wk after treatment. The effect of ZD1839 on EGFR function was assessed by Western blotting of EGFR and its phosphorylated form in CWR22 and variant tumors before and after treatment with this agent. ZD1839 at its max. tolerated dose (150 mg/kg) inhibited the growth of androgen-dependent CWR22 by 54%, and the growth of two variants with different degrees of androgen independence and androgen receptor gene expression (CWR22LD1 and CWR22RV1) by 76%. The effects of ZD1839 were similar to those recorded for phosphorylation of EGFR as detd. by Western blotting. Co-administration of ZD1839 at its max. tolerated dose markedly increased the antiproliferative action of the antiandrogen bicalutamide against CWR22LD1. In fact, combining ZD1839 with a suboptimal dose of bicalutamide was more effective than a higher dose of bicalutamide alone. Co-administration of ZD1839, which required a 2-3-fold attenuation of dose to avoid toxicity, also markedly increased the therapeutic activity of carboplatin and paclitaxel against CWR22RV1, bringing about regression to a degree not seen with either agent alone. Tumor-free mice were seen only with the combination of ZD1839 and paclitaxel.

The results obtained in these related and highly relevant models of human prostate cancer suggest that ZD1839 may

have a role in enhancing existing treatments of androgen-dependent and -independent forms of this disease in patients.

Answer 3:

Bibliographic Information

Switch from antagonist to agonist of the androgen receptor blocker bicalutamide is associated with prostate tumour progression in a new model system. Culig, Z.; Hoffmann, J.; Erdel, M.; Eder, I. E.; Hobisch, A.; Hittmair, A.; Bartsch, G.; Utermann, G.; Schneider, M. R.; Parczyk, K.; Klocker, H. Department of Urology, University of Innsbruck, Innsbruck, Austria. British Journal of Cancer (1999), 81(2), 242-251. Publisher: Churchill Livingstone, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 132:131907 AN 1999:658147 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Advanced prostate cancer is treated by androgen ablation and/or androgen receptor (AR) antagonists. To investigate the mechanisms relevant to the development of therapy-resistant tumors, the authors established a new tumor model which closely resembles the situation in patients who receive androgen ablation therapy. Androgen-sensitive LNCaP cells were kept in androgen-depleted medium for 87 passages. The new LNCaP cell subline established in this manner. LNCaP-abl, displayed a hypersensitive biphasic proliferative response to androgen until passage 75. Maximal proliferation of LNCaP-abl cells was achieved at 0.001 nM of the synthetic androgen methyltrienolone (R1881), whereas 0.01 nM of this compd. induced the same effect in parental cells. At later passages (> 75), androgen exerted an inhibitory effect on growth of LNCaP-abl cells. The non-steroidal anti-androgen bicalutamide stimulated proliferation of LNCaP-able cells. AR protein expression in LNCaP-abl cells increased approx. fourfold. The basal AR transcriptional activity was 30-fold higher in LNCaP-abl than in LNCaP cells. R1881 stimulated reporter gene activity in LNCaP-able cells even at 0.01 nM, whereas 0.1 nM of R1881 was needed for induction of the same level of reporter gene activity in LNCaP cells. Bicalutamide that acts as a pure antagonist in parental LNCaP cells showed agonistic effects on AR transactivation activity in LNCaP-abl cells and was not able to block the effects of androgen in these cells. The non-steroidal AR blocker hydroxyflutamide exerted stimulatory effects on AR activity in both LNCaP and LNCaP-abl cells; however, the induction of reporter gene activity by hydroxyflutamide was 2.4- to 4-fold higher in the LNCaP-abl subline. The changes in AR activity were assocd. neither with a new alteration in AR cDNA sequence nor with amplification of the AR gene. Growth of LNCaP-abl xenografts in nude mice was stimulated by bicalutamide and repressed by testosterone.

In conclusion, the results show for the first time that the non-steroidal anti-androgen bicalutamide acquires agonistic properties during long-term androgen ablation. These findings may have repercussions on the natural course of prostate cancer with androgen deprivation and on strategies of therapeutic intervention.